THE EFFECT OF CORTISONE AND ACTH ON THE PATHOGENESIS OF TUBERCULOSIS*

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In the study of the role of sex hormones in resistance to infection, it was noted that tuberculosis in rabbits is accompanied by a marked hypertrophy of the adrenal cortex.[1] Furthermore, in subsequent studies, it was found that the weight of the adrenals of the natively most resistant race in our rabbit colony affected by tuberculosis caused by the human-type tubercle bacillus is much greater than that of a susceptible race similarly infected.[2] Therefore, investigations on the role of the adrenal cortex in resistance to the disease were undertaken to determine whether resistance can be increased by increasing adrenal function and, conversely, whether by lowering this function the native resistance can be diminished.

When natively susceptible and resistant rabbits inhale a certain known number of virulent human-type tubercle bacilli, an extensive pulmonary tuberculosis is found, as a rule, five months after infection in the former, and none at all in the latter.[3] If such rabbits, thus quantitatively exposed, are killed five weeks after infection, the number of primary tubercles generated in these two types of animals is inversely proportional to their genetic resistance: the greater the resistance, the fewer the primary pulmonary foci (PLATE 1, FIGURE 1).

Methods and Materials

With the availability of cortisone, the following experiment was performed. Twenty litter mates of the genetically uniform and highly susceptible strain FC were divided into two groups of ten each. Total and differential counts of their blood cells and their fasting blood sugar were determined. At the same time, the spread of India ink and of rabbit hemoglobin in the skin was measured four hours after injection. The inflammation at the site of injection of these substances in the skin was ascertained on the next day. Having obtained these base lines, ten of the rabbits received two mg. of cortisone acetate per kilogram intramuscularly on alternate days. The ten control litter mates received the same volumes of the suspending medium without the cortisone by the same route, at the same intervals. Three days after the beginning of cortisone treatment, when the absolute number of circulating lymphocytes in the blood of the experimental animals had been markedly depressed, and when the fasting blood sugar of the same animals had increased by comparison with the essentially unchanged levels of these items in the control animals, both groups were simultaneously exposed to the quantitative inhalation of known numbers of viable, virulent, human-type tubercle bacilli, H37Rv, in the ap-

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paratus for experimental air-borne infection, which has been carefully evaluated as previously described.[4]

After the control and experimental animals were infected, the cortisone and the suspending medium, respectively, were administered to each group at the same intervals and in the same amounts, as stated above, throughout the course of the experiment. During this time, the absolute number of circulating lymphocytes of the blood, the fasting blood sugar, the blood ascorbic acid, the development of tuberculin sensitivity and antibodies against the tubercle bacillus, the spread of India ink and rabbit hemoglobin in the skin, and the inflammation induced by these agents in this tissue were measured. At this time, the excretion of steroids in the urine was also determined.

TABLE 1

THE EFFECT OF CORTISONE ON THE DEVELOPMENT OF THE TUBERCULIN REACTION IN THE SKIN AT DIFFERENT INTERVALS FOLLOWING THE INHALATION OF HUMAN-TYPE TUBERCLE BACILLI

Rabbit number		Inflammation 16–18 days after infection, cu.mm.		Inflammation 21 days after infection, cu.mm.		Inflammation 25–27 day after infection, cu.mm.	
Nontreated	Treated	Non-treated	Treated	Nontreated	Treated	Nontreated	Treated
C 11	E 1	13	0	288	0	391	14
C 12	E 2	17	0	126	12	175	23
C 13	E 3	7	0	530	26	608	14
C 14	E 4	10	0	216	16	288	27
C 15	E 5	95	0	152	0	315	21
C 16	E 6	6	0	54	0	240	10
C 17	E 7	0	0	18	0	68	14
C 18	E 8	8	0	190	0	373	11
C 19	E 9	11	0	92	11	152	21
C 20	E 10	0	0	15	0	83	0
Mean		17 ± 8	0 P = 0.025	168 ± 47	7 ± 3 P = 0.001	269 ± 49	16 ± 2 P = 0.000

Results of Cortisone Treatment

It was found that the absolute number of circulating lymphocytes of the cortisone-treated animals was continuously diminishing, in statistically significant amounts, with continuation of treatment, while that of the controls actually increased, as compared with their respective base lines. Likewise, the fasting blood sugar of the experimental animals increased with the duration of treatment while, in the controls, this increment was much less.

The spread of India ink or hemoglobin in the skin was not definitely affected in either the control or the experimental animals. The inflammation induced by these agents in the skin was markedly reduced in the experimental as compared with control animals, however, and in statistically significant amounts. Likewise, tuberculin produced much more inflammation in the control than in the cortisone rabbits (TABLE 1). This is clearly due to the protective effect exercised by cortisone on the capillaries against agents that increase their permeability, as observed by Menkin. Peptone, which releases fibrinolysin

in vitro, increases the permeability of the capillaries of normal rabbits to a much greater extent than it does in cortisone-treated animals, (PLATE 1, FIGURES 2a & 2b). Moreover, pure fibrinolysin, a substance released at sites of inflammation, causes marked leakage of the vessels of normal rabbits and scarcely affects cortisone-treated animals, when injected into the skin. Furthermore, the capillary fragility of cortisone-treated rabbits is much less than that of untreated controls, as indicated by capillary hemorrhage induced by applying a uniform suction to the skin, (PLATE 1, FIGURES 3a & 3b). These observations would indicate that cortisone not only protects the capillary wall against chemical agents that disrupt its integrity, but that the tensile strength of this wall against the internal blood pressure is also augmented by the hormone. Both these effects may be the result of physical changes in the ground substance induced by the hormone.[5]

The antibody production against the tubercle bacillus, as revealed by the Middlebrook and Dubos hemagglutination test, was not conspicuously affected, although the titer in the experimentals was slightly though uniformly lower than in the controls.

In view of the demonstration by Gordon and Katsh[6] that starvation, by stimulating the adrenal function, increases the phagocytic activity of the macrophages, half of the control and experimental rabbits were given 6 cc. of a 1:3 dilution of India ink in saline per kilogram intravenously, three hours before they were killed by air embolism on the 34th and 36th day after infection. Another group of three cortisone-treated and three untreated rabbits were similarly injected and killed two weeks after infection. Their livers and spleens were digested with concentrated KOH, and the weight of carbon present in them was determined. Histological preparations of these organs were also studied. It was found that the phagocytosis of carbon particles was markedly increased in the cortisone-treated animals, (PLATE 2, FIGURES 4 and 5). Similarly, tubercle bacilli injected intravenously were more completely removed from the circulation of the treated rabbits, within five minutes after their introduction, than from that of the controls, and the number of bacilli retained in the spleens of the former was correspondingly greater (TABLE 2). The remaining rabbits were killed 35 or 38 days after inhalation. In all cases, each cortisone-treated rabbit was killed on the same day following infection as its control litter mate that had inhaled the same infected air, for the same time, at the same sitting. All animals were starved for 17 hours before they were killed. The glycogen present in the livers of all control and experimental animals was determined, and the weights of the liver, spleen, adrenals, gonads, and pituitary were ascertained.

It was found that the livers of the cortisone-treated rabbits were twice as heavy as those of the controls. This was due to excessive deposits of glycogen and fat in the markedly enlarged liver cells of the experimental animals, obviously due to the physiological effects of the cortisone. The spleens of the cortisone rabbits were markedly reduced in weight, as a result of the lympholytic effect of cortisone, demonstrable even two weeks after infection.[2] The adrenals were markedly atrophied in the experimentals, clearly due to the suppression of the secretion of ACTH by the pituitary, produced by the high

level of cortisone in their blood. The thyroids of the experimental rabbits were uniformly, though only moderately, reduced in weight.

It is clear from these results that the experimental animals were under the intense pharmacologic effects of cortisone and that this hormone had modified the remaining functions of the markedly atrophied fascicular and reticular zones of the adrenal cortex as well as the functions of other glands of internal secretion.

The number and size of the tubercles developed in the lungs of the control and experimental rabbits were accurately determined. The number of tubercles generated in the cortisone rabbits was uniformly greater than in the controls. On the average, three to four times as many tubercles resulted from the inhalation of human tubercle bacilli by cortisone-treated rabbits as from the inhalation of the same numbers of bacilli by untreated litter mates of the same

TABLE 2

NUMBER OF TUBERCLE BACILLI IN THE BLOOD AND SPLEEN OF NORMAL AND CORTISONE-TREATED RABBITS AT DIFFERENT INTERVALS FOLLOWING THE INTRAVENOUS INOCULATION OF THE SAME SUSPENSION OF H37Rv IN UNIT VOLUMES PER KILOGRAM OF BODY WEIGHT

Rabbit number		Blood, no. of bacilli per cc.				Spleen, no. of bacilli per mg.	
		5 minutes after injection		22 hours after injection		22 hours after injection	
Normal	Treated	Normal	Treated	Normal	Treated	Normal	Treated
A 12-12	A 10-3	260,000	157,000	140	1,300	2,200	5,600
A 9-142	A 9-132	183,000	183,000	1,200	130	2,400	3,000
A 12-13	A 12-19	280,000	86,000	486	2,400	4,200	5,500
A 12-14	A 12-29	15,000	7,600	31	110	277	658
A 13-8	A 13-9	16,000	8,500	18	11	200	272
Average		150,800	88,420	375	790	1,855	3,006

inbred strain and the same genetic resistance to the infection. This difference is statistically significant (PLATE 2, FIGURE 6).

The size of the tubercles in the lung, however was uniformly and markedly reduced in the cortisone-treated animals. In the untreated rabbits, the yellow-gray caseous center was surrounded by a wide ring of grayish translucent infiltration; while in the experimental litter mates, on the other hand, there was scarcely any infiltration about the almost-white caseous foci situated nakedly in the unaffected lung parenchyma. Furthermore, the spread of the disease to the draining tracheobronchial lymph nodes and to the internal organs was markedly reduced in the experimental rabbits.

It was found in these experiments as well as in others not detailed here that, initially, notwithstanding the demonstrated greater *in vivo* phagocytic capacity afforded the reticuloendothelial cells by cortisone, the number of inhaled bacilli arrested in the lung of the experimental rabbits was no greater than that retained by the controls.

Two weeks after infection, the bacilli were more numerous in the lungs of the cortisone rabbits as observed both histologically and by culture, (PLATE 2,

FIGURES 7 and 8.) In the draining tracheobronchial lymph nodes of the controls, however, they greatly outnumbered those of the experimental animals (TABLE 3).

Five weeks after exposure, the pulmonary lesions in the cortisone rabbits were sharply delimited foci of caseous pneumonia with intra-alveolar plugs of partially caseated cells still retaining their pyknotic nuclei and swarming with inordinate numbers of bacilli. There was little interstitial or perifocal inflammation. These caseous plugs were largely out of contact with the lung parenchyma and its blood and lymph circulation (PLATE 3, FIGURES 9 and 10). The lesions in the controls were tuberculous granulomas with well-advanced, discrete caseous centers from which all cellular boundaries and nuclei had disappeared and which contained moderate numbers of bacilli surrounded by widely spreading zones of infiltrating perifocal inflammation, penetrated by ingrowing capillaries (PLATE 3, FIGURES 11 and 12). These important differences in the histologic character of the lesions in the two types of animals accord

TABLE 3

NUMBER OF TUBERCLE BACILLI CULTURED FROM 2 MG. OF LUNG AND FROM DRAINING TRACHEOBRONCHIAL NODES OF CONTROL AND CORTISONE-TREATED RABBITS TWO WEEKS AFTER SIMULTANEOUS INHALATION OF HUMAN-TYPE TUBERCLE BACILLI

Rabbit number		Lungs		Tracheobronchial nodes	
Control	Experimental	Control	Experimental	Control	Experimental
Ca 5-10	Ca 5-9	103	877	21	2
Ca 5-21	Ca 5-20	191	360	30	9
Ca 5-19	Ca 5-47	224	305	68	0.7

well with the gross differences between them described above. Thus, though the bacilli in the pulmonary lesions of the untreated animals were far fewer than in the experimental rabbits, invasion of the blood and lymph by the bacilli occurred more frequently in the former than in the latter (PLATE 4, FIGURES 13 and 14). Similar observations have been made in a more resistant strain of rabbits, AD, exposed to bovine bacilli of reduced virulence.

Much of the difference in the pathogenesis of tuberculosis in the two types of animals may be understood on the basis of the two observed effects of the hormone: (1) Pharmacologic doses of cortisone markedly interfere with the digestive capacity of the macrophages for the ingested bacilli. (2) Cortisone, by virtue of the protection it affords the capillaries against agents that increase capillary permeability and, hence, its antiphlogistic effect conspicuously influences the character of the lesion, its extent, and its dissemination in the body. The former explains the genesis of greater numbers of primary tubercles occurring in the treated animals. It must be clearly understood that present evidence[3] indicates that the majority of human-type tubercle bacilli ingested by the alveolar phagocytes of even a very susceptible rabbit are soon destroyed and do not accumulate sufficiently within these cells to generate a grossly visible tubercle. Cortisone, by interfering with the di-

gestive capacity of these cells, allows many more bacilli to multiply sufficiently within the alveolar phagocytes to yield visible primary foci. The antiphlogistic influence of the hormone explains not only the suppression of the perifocal inflammation about the intra-alveolar plugs swarming with tubercle bacilli in the cortisone rabbits and the marked reduction of the tuberculin reaction in these rabbits, but also the partial localization of the disease at the portal of entry, for the suppression of the inflammation retards the ingrowth of capillaries and lymphatics into the isolated alveolar plugs where the bacilli swarm. Hence, withdrawal of cortisone reverts the sensitivity of the capillary walls to agents that increase permeability to its original state, with the consequent intensification of the tuberculin reaction and the development of an intense perifocal inflammation about the accumulated masses of bacilli in the lungs that had resulted from the previous hormone treatment (PLATE 4, FIGURE 15). This led to massive consolidating pulmonary tuberculosis with liquefaction, rupture into the bronchi, hematogenous dissemination and a fatal issue in natively susceptible rabbits, and to progressive disease with cavity formation in natively resistant rabbits. At this time, the lesions in the simultaneously infected untreated rabbits were rapidly regressing in the susceptible rabbits and had completely healed in most of the resistant animals.[2]

No evidence has thus far been obtained to indicate that the inordinate accumulation of the tubercle bacilli in the cells of the cortisone-treated rabbits can be accounted for by a stimulating effect of the hormone on the growth of the bacilli. Cortisone, in the concentration present in the body of the experimental animals, did not enhance the growth of tubercle bacilli *in vitro*. The extracellular multiplication of the bacilli *in vivo* was markedly suppressed when bacilli within collodion-coated silk bags were placed into the peritoneal cavity of hormone-treated rabbits. Yet, one of the most significant effects of pharmacologic doses of cortisone in tuberculosis is its profound influence on the physiology of the macrophages. While the hormone affords these cells increased phagocytic activity, their digestive capacity for the ingested bacilli is markedly depressed.

The Effect of ACTH

It was noted above that the pharmacologic doses of cortisone used in these experiments caused marked atrophy of the fascicular and reticular zones of the adrenal cortex and, hence, necessarily modified their functions. Since tuberculosis in resistant races is associated with hypertrophy of the adrenal cortex, it is possible that physiologic rather than pharmacologic doses of these and other adrenocortical and hypophyseal hormones may actually enhance the defense mechanisms against infection.

To determine what effect physiological stimulation of the adrenal cortex has on resistance to tuberculosis, two susceptible strains of rabbits were chosen, one, the FC race reported above, and the other, the C strain. The latter differs from the FC strain in that its adrenals are genetically much larger than those of the former. Both strains were divided into two groups. The first group received daily intramuscular injections of sheep ACTH in gelatin for 3 days, 0.5 mg. per kilo. The control litter mates received saline by the same route. Both groups were then simultaneously exposed to the quantitative inhalation

TABLE 4

THE EFFECT OF 0.5 MG. OF SHEEP ACTH IN GELATIN DAILY PER KILO OF BODY WEIGHT ON THE NUMBER OF PRIMARY PULMONARY TUBERCLES GENERATED BY THE QUANTITATIVE INHALATION OF H37Rv IN THE SUSCEPTIBLE FAMILIES FC AND C, RESPECTIVELY

Rabbit number	Weight of adrenals mg./100 g.	Weight of liver g./100 g.	Number of bacilli inhaled estimated	Number of tubercles generated	No. of bacilli yielding one tubercle
FC family, control					
FC 4-9	12.8	2.1	20,618	671	31
FC 2-48	6.4	2.2	53,821	1,442	37
FC 4-24	17.1	2.4	20,935	341	61
FC 4-17	7.9	1.7	45,237	632	71
FC 4-30	16.0	2.1	38,748	345	112
Mean	12.0 ± 1.9	2.1 ± 0.11			62 ± 14*
FC family, treated					
FC 4-18	12.7	2.3	41,715	486	86
FC 4-21	18.9	2.6	20,935	223	94
FC 2-52	14.4	2.2	47,390	477	99
FC 4-16	12.1	2.1	44,125	357	124
FC 4-15	15.2	2.6	20,776	140	148
Mean	14.7 ± 1.1	2.3 ± 0.10			110 ± 11*
C family, control					
C 12-16	22.3	2.2	45,359	1,187	38
C 12-20	28.7	2.4	13,062	313	42
C 12-1	28.0	2.3	35,411	833	43
C 12-18	23.0	2.8	12,502	262	48
C 12-28	20.6	2.8	21,252	323	66
Mean	24.5 ± 1.4	2.5 ± 0.13‡			47 ± 4†
C family, treated					
C 12-12	26.0	4.1	47,051	1,672	28
C 12-24	24.1	3.1	11,755	297	40
C 11-20	30.9	2.8	36,709	789	47
C 12-27	21.9	3.2	20,142	308	65
C 12-17	26.6	3.2	13,248	190	70
Mean	25.9 ± 1.3	3.3 ± 0.18‡			50 ± 7†

* C. R. of the difference between these figures is 2.7 with "P" value of 0.01.
† The difference between these two figures is not significant.
‡ C. R. of the difference between these figures is 3.6 with a "P" value of 0.004.

TABLE 5

THE EFFECT OF 0.5 MG. OF PORCINE ACTH IN GELATIN DAILY PER KILO OF BODY WEIGHT ON THE NUMBER AND SIZE OF PRIMARY PULMONARY TUBERCLES GENERATED BY THE QUANTITATIVE INHALATION OF H37Rv IN THE SUSCEPTIBLE FAMILY FC

Rabbit number	Weight of adrenals, mg./100 g.	Weight of liver, g./100 g.	No. of bacilli inhaled (estimated)	No. of tubercles generated	No. of bacilli yielding one tubercle	Average diameter of tubercle, mm.	Rabbit number	Weight of adrenals, mg./100 g.	Weight of liver g./100 g.	No. of bacilli inhaled (estimated)	No. of tubercles generated	No. of bacilli yielding one tubercle	Average diameter of tubercle, mm.
	Control							*Treated*					
FC 4-13	17	1.6	23,866	635	38	5.0	FC 4-14	13	3.1	23,694	1,350	18	3.0
FC 4-4	17	1.6	26,270	530	49	4.4	FC 5-6	8	2.2	22,606	517	44	2.5
FC 5-7	13	2.2	21,865	440	50	3.5	FC 4-32	11	2.7	28,165	571	49	3.0
FC 4-29	12	2.5	25,015	359	70	3.1	FC 5-2	16	2.0	21,865	401	54	3.9
FC 6-8	16	2.2	33,998	445	76	3.6	FC 4-31	14	2.5	24,553	434	56	2.4
FC 4-33	11	1.9	27,980	330	85	3.2	FC 6-3	29	1.9	37,998	605	63	3.3
FC 6-1	16	1.9	37,141	408	93	3.0	FC 6-7	18	2.3	34,569	391	88	2.5
FC 4-26	10	1.7	27,128	273	99	3.0	FC 4-11	19	3.7	23,866	125	191	2.8
FC 5-11	7.5	1.9	36,855	209	176	4.5							
Mean	13.3 ± 1.2	1.9 ± 0.1*			82 ± 14	3.7 ± 0.23†		16 ± 2.3	2.5 ± 0.2*			70 ± 19	2.9 ± 0.18†

* The "P" value of the difference between these observation is 0.008.
† The "P" value of the difference between these observation is 0.007.

of human-type tubercle bacilli. The ACTH and the saline treatment, respectively, were continued throughout the experiment. The only evidence of a possible physiological effect of the ACTH in the FC rabbits was a constant polymorphonuclear leukocytosis. While the lymphocytes tended to be suppressed by the hormone, this effect was not uniform. In the FC race neither the weight of the liver nor its glycogen content was affected by this ACTH preparation. In the C race, however, the same preparation in the same amounts caused a statistically significant increase in liver weight and a definite increment in the glycogen deposited in the liver (TABLE 4). In other words, the sheep ACTH used contained an insufficient amount of corticotropin to stimulate an excess secretion of physiologically detectable cortisonelike steroids from the small adrenals of the FC family but enough to cause an excess of physiologically detectable steroid from the genetically large adrenals of the C family. It was, therefore, of interest to find that this ACTH treatment increased the resistance of the FC rabbits and reduced the number of tubercles generated by about one half (TABLE 4 and PLATE 4, FIGURE 16). It had no effect on the C rabbits. This would suggest that the beneficial effect of the ACTH treatment in the FC rabbits is not due to an excess secretion of glucocorticoids.

In another experiment (TABLE 5), the same FC strain, with its genetically small adrenals, was treated with the same dose of a porcine ACTH in gelatin. This ACTH preparation caused a marked increase in liver glycogen and a significant increment in liver weight, thus eliciting an excess secretion of oxycorticosteroids. It is noteworthy, therefore, that this corticotropin simulated to some extent the effect of cortisone on the pathogenesis of the disease by slightly increasing the number of tubercles generated and reducing their size.

Summary

Cortisone affects in a fundamental fashion all the essential mechanisms involved in the pathogenesis of tuberculosis. It increases the accumulation of tubercle bacilli within the macrophages though their phagocytic activity is enhanced. It suppresses nonspecific and allergic inflammation as a result of the protective effect exerted by the hormone against many agents that increase capillary permeability. This antiphlogistic influence, by suppressing the migration of cells to and from the tubercles, and by reducing the ingrowth of capillaries into these foci, interrupts the bridge between the lesion and the rest of the body and tends to isolate it partially and to localize it temporarily and incompletely at the portal of entry. The reduced capillary permeability and the lympholytic effect of the hormone may also be instrumental in the retardation of the development of the caseous process and the diminution of antibody production, which is characteristic of the cortisone-treated animals; for allergic sensitization, of which caseation is a part, has now been demonstrated to be at least partly mediated by antibodies.[7] Lymphocytes are probably concerned in antibody production,[8] and the transport of antigens and antibodies is influenced by inflammation. Studies directed to elucidate the effect of cortisone on the intercellular ground substance, on cellular permeability, and on the enzyme functions of the phagocytes are most desirable.

Thus, in tuberculosis, cortisone acts like a double-edged sword. The very

suppression of the inflammation, while it tends to isolate the infection from the rest of the body, nevertheless permits the local multiplication of the bacteria, for the phagocytes and the humoral agents concerned with combatting the infection arrive tardily and in low concentration. Furthermore, there is general agreement that cortisone administered during the course of immunization tends to lower antibody production, which would also militate against the host. Again, while there is ample evidence that increased adrenal function and cortisone stimulate phagocytosis of particulate matter and bacteria, the digestive capacity of the cells for the ingested microorganisms is markedly reduced, whether these be tubercle bacilli, pneumococci, streptococci, or even red blood cells.[9] Hence, the bacteria can accumulate in the tissues in the absence of symptoms of fever and toxemia, which are suppressed by the hormone.

The significance of the ACTH treatment reported in this study is not quite clear at present. Nevertheless, it would appear that by suitable, sheep ACTH stimulation, the resistance of certain animals whose adrenal function, as indicated by their mass, is low can be increased by corticotropin; whereas similar treatment of rabbits with higher natural adrenal function exercises no effect. Furthermore, even in rabbits with low adrenal function, beneficial effects from ACTH can be obtained only within very narrow limits. A corticotropin of greater potency may induce cortisone effects that nullify the protective influence that may stem from corticotropin. Much further investigation is necessary to establish this interpretation.

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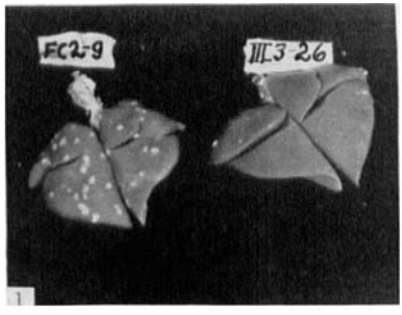

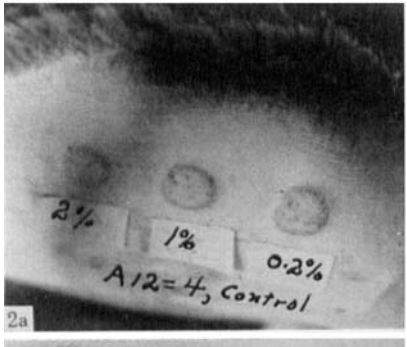

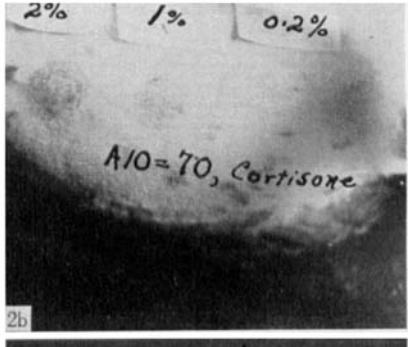

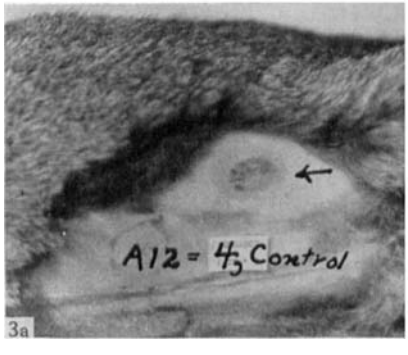

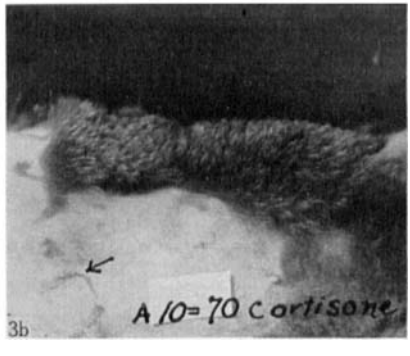

PLATE 1

FIGURE 1. The lungs of susceptible rabbit FC 2-9 and of a resistant rabbit III 3-26, 32 days after the simultaneous inhalation of 4200 to 4300 human type tubercle bacilli. One of 39 inhaled human-type bacillary units generated a primary tubercle in the susceptible animal, while only one of 1000 inhaled bacillary units gave rise to a pulmonary focus in the resistant animal.

FIGURE 2a. Extravasation of intravenously injected trypan blue at the sites of the intracutaneous injection of 2, 1, and 0.2 per cent peptone, respectively, in the untreated rabbit A 12-4.

FIGURE 2b. In the cortisone-treated rabbit, A 10-70, the trypan blue extravasated to a considerable extent only at the site of injection of 2 per cent peptone. A trace of the dye left the vessels at the site of injection of 1 per cent of the irritant, while none left the vessels at the site of injection of 0.2 per cent peptone.

FIGURE 3a. Capillary hemorrhage, indicated by the arrow, at the site of suction in the skin of the normal rabbit, A 12-4.

FIGURE 3b. No capillary hemorrhage in the cortisone-treated rabbit, A 10-70, at the site of application of the same degree of suction for the same time as in the normal rabbit shown in FIGURE 3a. This site is indicated by the ring and arrow.

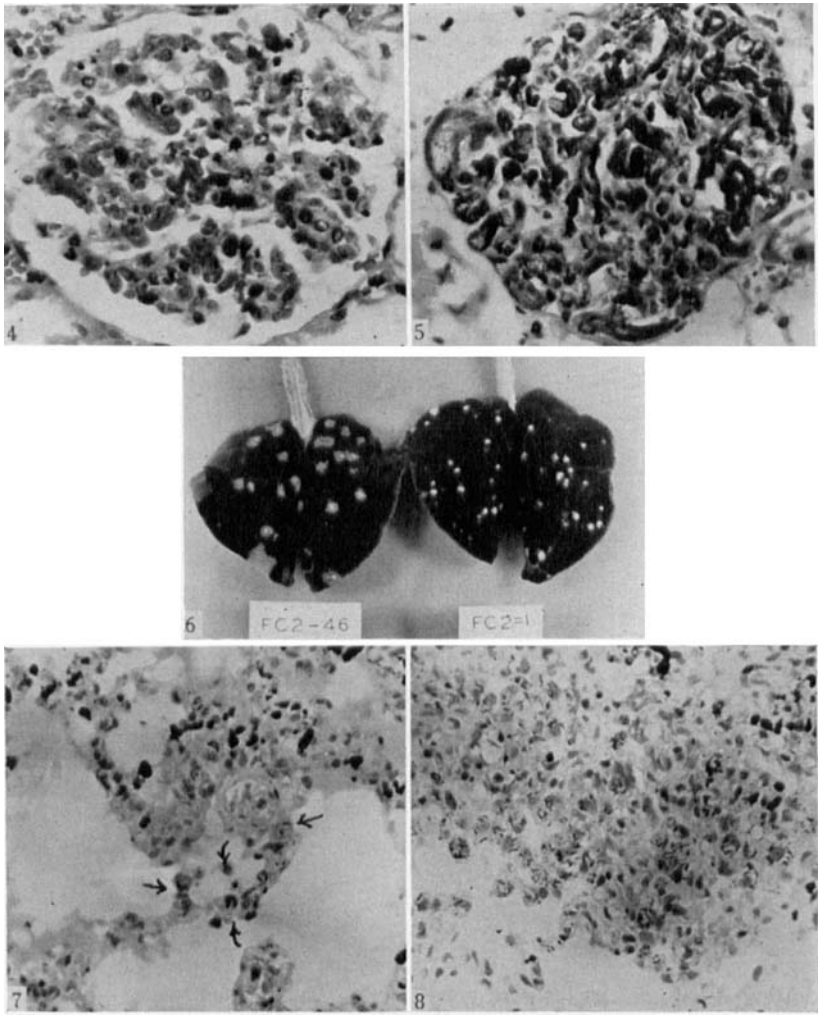

PLATE 2

FIGURE 4. Scant phagocytosis of carbon particles by the cells of the kidney glomerulus of the untreated rabbit, Ca 5-10, 18 hours after the intravenous injection of 6 cc. per kilo of a 1:3 dilution of India ink.

FIGURE 5. Intense phagocytosis of carbon particles by the cells of the kidney glomerulus of the cortisone-treated rabbit, Ca 5-20, given the same amount of the same suspension of India ink per kilo and killed at the same interval after the intravenous injection as Ca 5-10 shown in FIGURE 4.

FIGURE 6. The lungs of the untreated rabbit, FC 2-46, and of the cortisone-treated rabbit, FC 2-1, 34 days after the simultaneous quantitative inhalation of human type tubercle bacilli. Both lungs are black from the intravenous injection of India ink. The tubercles in the control rabbit are much fewer than in the treated animal. 81 inhaled bacilli were necessary to generate one pulmonary tubercle in the former, while 39 microorganisms were sufficient for the latter. The size of the tubercles are markedly smaller in the cortisone rabbit, however. In the untreated rabbit, the yellowish-white caseous centers are surrounded by a wide ring of translucent gray infiltration. In the experimental rabbit, there is scarcely any infiltration about the brightly white caseous foci situated nakedly in the unaffected lung parenchyma.

FIGURE 7. One of the rare primary foci in the lung of the untreated rabbit, Ca 5-10, 2 weeks after a quantitative inhalation of human-type tubercle bacilli. The arrows indicate the meager bacilli in this earliest microscopic evidence of the intracellular growth of the microorganism in a control animal.

FIGURE 8. One of the much larger and more common primary foci in the lung of the cortisone-treated rabbit, Ca 5-9, a litter mate of Ca 5-10 shown in FIGURE 7. Both rabbits were killed 2 weeks after a simultaneous quantitative inhalation of human-type bacilli. Numerous intracellular tubercle bacilli are found. There is no lack of phagocytosis. The accumulation of tubercle bacilli in the mononuclears of the cortisone-treated rabbit is far greater than that in the phagocytes of the untreated control animal.

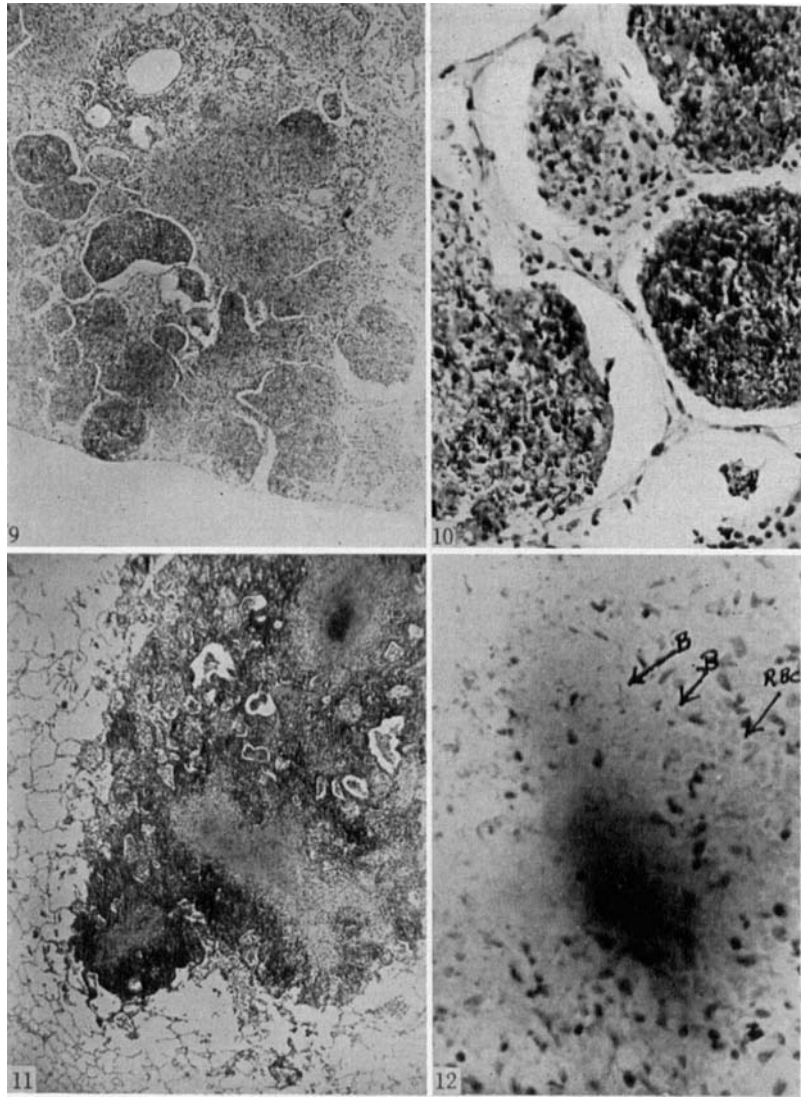

PLATE 3

FIGURE 9. The lung of the cortisone-treated rabbit, FC 3-39, 35 days after the quantitative inhalation of human bacilli, showing an area of caseous pneumonia with intra-alveolar plugs of partially caseated cells.

FIGURE 10. A higher magnification of the same lung as depicted in FIGURE 9 showing the swarming of inordinate numbers of bacilli in the necrotic alveolar plugs. Note that these plugs are not contiguous with the alveolar septa. These septa are extremely thin and not infiltrated or inflamed.

FIGURE 11. The lung of FC 3-37, an untreated litter mate of rabbit FC 3-39, shown in FIGURES 9 and 10. Both rabbits were killed at the same time after the simultaneous inhalation of human-type bacilli. The lung of the untreated rabbit shows a tuberculous granuloma with well-advanced caseous centers surrounded by a widely spreading zone of infiltrating perifocal inflammation.

FIGURE 12. The lung of FC 2-47, an untreated rabbit, killed 34 days after the quantitative inhalation of human-type bacilli. The periphery of a far-advanced caseous center with complete disappearance of cellular structures is seen. Occasional bacilli are indicated by the arrows marked B. Hemorrhage from a ruptured capillary, indicated by the arrow marked RBC, is in close proximity to the bacilli.

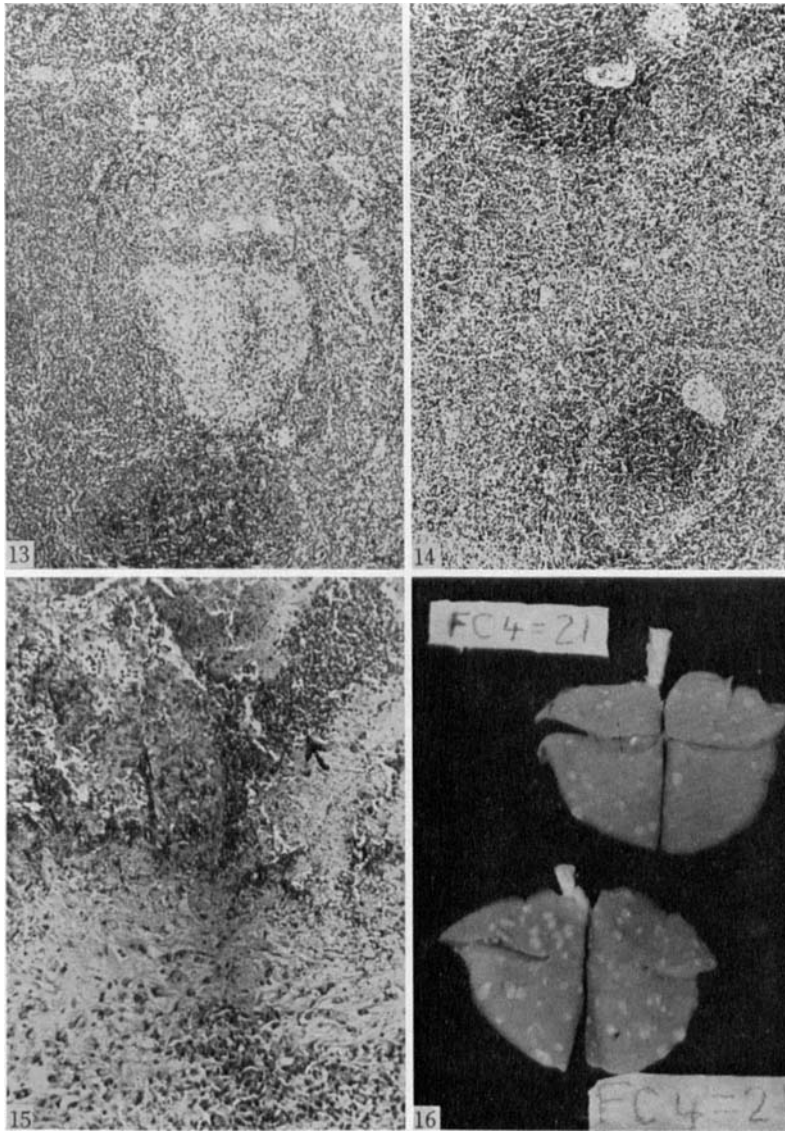

PLATE 4

FIGURE 13. The spleen of the untreated rabbit, FC 3-29, killed 38 days after the quantitative inhalation of human-type tubercle bacilli. A large hematogenous tubercle is seen.

FIGURE 14. The spleen of the cortisone-treated rabbit, FC 3-30, killed at the same time after the same quantitative inhalation of human-type tubercle bacilli as the control rabbit, FC 3-29, shown in FIGURE 13. There is no hematogenous tuberculosis in this spleen.

FIGURE 15. The lung of rabbit Ca 4-7, which had inhaled about 16,000 tubercle bacilli of the human type. The rabbit was under the influence of cortisone for 45 days. The hormone was then withdrawn and the rabbit died 34 days later of massive caseous pneumonia, liquefaction, and bronchial and hematogenous dissemination. The withdrawal of the hormone induced a severe perifocal inflammation, indicated in the lower half of the photograph, about the caseous plugs swarming with bacilli that had resulted from the previous cortisone-treatment. These caseous plugs are shown at the top of the microphotograph. Areas of liquefaction are shown by the arrow where there is an intense polymorphonuclear infiltration.

FIGURE 16. The lungs of FC 4-21 and its litter mate FC 4-24, both of which had inhaled about 21,000 human type tubercle bacilli, simultaneously. Both rabbits were killed 31 days after exposure. In FC 4-21, treated with sheep ACTH in gelatin, 94 inhaled bacilli yielded one tubercle. In the untreated control rabbit, FC 4-24, 61 inhaled bacilli generated one pulmonary focus.